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ATTENTION: 8(D) HEALTH AND SAFETY REPORTING RULE (REPORTING)

Dear Sir or Madam:

As required by 40 CFR 716 as amended, we herewith submit a copy of the following recently completed health and safety study.

Neurotoxicologic Examination of Fischer 344 Rats Exposed to 1,2-Dichloropropane (DCP) Via Gavage got Two Weeks

Chemical Name	CAS Number
1,2-dichloropropane	78-85-5

This study was conducted in preparation for a neurotoxicological study required for dichloropropane under a TSCA Section 4 rule (40 CFR 799.1550).

The Dow report identification number, **D0002861**, has been marked at the top of the title page of the report. Please refer to this Dow identification number in any communication regarding this study. **The enclosed report does not contain Dow Confidential Business Information.**

Very truly yours,

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enclosure

cc: Lynn Marcus (TS-793) Room NEG004T
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NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2- DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS

Authors

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Final Report

February 10, 1989

Performing Laboratory

Mammalian and Environmental Toxicology Research Laboratory
Health and Environmental Sciences
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Midland, Michigan 48674

Laboratory Project Study ID

Irrelevant, Filing Data

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The probe study reported herein was conducted in compliance with the following GLP regulations.

United States Environmental Protection Agency,
Title 40 Code of Federal Regulations Part 792,
Federal Register. 29 November 1983

Japan Ministry of Agriculture, Forestry and Fisheries,
59 Nohsan, Notification No. 3850,
Agricultural Production Bureau,
10 August 1984

Organization for Economic Co-Operation and Development
ISBN 92-64-12367-9, Paris 1982

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QUALITY ASSURANCE STATEMENT

STUDY TITLE: NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS

This study was examined for conformance with Good Laboratory Practices as published by the U.S. Environmental Protection Agency, and the Food and Drug Administration. The final report was determined to be an accurate reflection of the data obtained. The dates of Quality Assurance activities on this study are listed below.

Study Start Date: 8 Jan, 1988 Date of Final Report: 10 Feb 1989

TYPE OF AUDIT:	DATE OF AUDIT:	DATE FINDINGS REPORTED TO STUDY DIRECTOR/MANAGEMENT:
Preliminary protocol	30 Dec, 1987	30 Dec, 1987
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Study conduct	9 Feb, 1988	9 Feb, 1988
Protocol, data, and draft report	6 Dec, 1988	8 Dec, 1988

ARCHIVING: Raw data and a copy of the final report are filed in the testing facility archives.

T. S. Gushow 10 Feb 89

T. S. Gushow, B.S.
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SUMMARY

A 2-week probe study of 1,2-dichloropropane (DCP) was conducted using groups of ten Fischer 344 rats per sex to aid in selecting doses for a subsequent 13-week study. Dose levels were 0 (control, corn oil), 300 or 500 mg/kg/day via gavage for 14 consecutive days. Data were obtained on body weight, clinical effects, body temperature, functional observational battery (FOB; 0, 1 hr, 6 hr, 24 hr, 7 day and 14 day recordings), motor activity, hematology, liver, kidney and spleen weights, gross pathology, and histopathologic examination of the liver and kidneys.

Gavage administration of 300 or 500 mg/kg/day of DCP to groups of ten rats per sex for 2 weeks produced treatment effects on demeanor manifested primarily as tearing, blinking and lethargy. These were pronounced following dosing only for the first few days of the study and thereafter control and treated rats appeared comparable. Other than these transient clinical effects, other treatment-related effects were generally of greater degree in male rats. Body weights, both during the study and at termination, of both groups of treated male rats were significantly decreased whereas only the high dose female rats had slightly decreased body weight.

The body temperature of male and female rats given either 300 or 500 mg/kg DCP was decreased 0.3-0.5° C when recorded approximately 1 hour after dosing on day 13. Observations noted in most animals for the FOB at 1 hour after the initial dose were tearing and blinking. Lethargy was also noted in some male and female rats and decreased respiration in female rats. No statistically significant effect was seen on motor activity of either sex when evaluated approximately 0.5 hour after dosing on day 14. Female rats, however, exhibited a dose-related trend for reduced activity. There were no effects on hematologic parameters considered related to treatment. Liver and kidney weights were increased in a general dose response manner for treated rats of either sex. Also, spleen weights were decreased in treated rats, particularly males. The decreased spleen weights were considered a nonspecific secondary effect of stress.

Histopathologic changes attributed to treatment were confined to the liver and noted for both males and females given either 300 or 500 mg DCP/kg/day. The changes were mild and were characterized by prominent nucleoli of the hepatocytes in the centrilobular region of the hepatic lobule, degeneration, and necrosis of individual hepatocytes accompanied by a few inflammatory cells. No microscopic effects were noted in the kidneys.

INTRODUCTION

The Environmental Protection Agency (EPA) identified 1,2-dichloropropane (DCP) for additional toxicological testing under Section 4(a) of the Toxic Substances Control Act (EPA, 1986, 1987). Included in the test rule was a requirement for an assessment of potential neurotoxicity which had the following components (applicable TSCA test guideline, EPA, 1985): functional observational battery (FOB) including grip strength (#798.6050), motor activity (#798.6200) and neuropathology (#798.6400).

Presented in this report are the results of a 2-week gavage probe study at dose levels of 0, 300 and 500 mg DCP/kg body weight/day that includes data on the FOB (without grip strength) and motor activity. The dose levels for the 2-week study were selected after a review of studies reported in the literature, and results from an acute and 7-day gavage probe study conducted in this laboratory. A summary of these data follows:

The oral acute, subacute and subchronic toxicity of DCP in male Sprague-Dawley rats has been evaluated by MacKenzie et al. (1987) and Bruckner et al. (1988). Rats received 100, 250, 500 or 1000 mg DCP/kg bw by gavage for 1, 5 or 10 days. After 1 day, only slight microscopic liver changes were noted at the high dose whereas at 5 days there was dose-dependent hepatic centrilobular degeneration, necrosis, inflammation and early fibrosis; these changes were less severe at 10 days compared to 5 days. Nucleolar enlargement of hepatocytes was seen at all dose levels at both 5 and 10 days, as was hemolytic anemia which increased in severity with increasing dose. Transient narcosis was observed at the lowest two dose levels and persistent sedation at the higher dose levels. In the subsequent subchronic study, rats were gavaged with 100, 250, 500 or 750 mg DCP/kg, 5 days/week for up to 90 days. The 750 mg/kg dose produced reduced food and water intake and cachexia (via narcosis) and over 50% of the high dose animals died within 10 days necessitating termination of the 750 mg/kg dose level. The highest two dose levels caused hepatic changes, testicular degeneration, adrenal cortical

lipidosis and meduliary vacuolization. Hemolytic anemia was reported at all four dosage levels.

Subchronic data in Fischer 344 rats also were generated by the National Toxicology Program (1983) in preparation for a carcinogenicity study. Dose levels were 0, 60, 125, 250, 500 or 1000 mg/kg bw 5 days/ week and were administered for 13 weeks via gavage using corn oil as the vehicle. All rats receiving 1000 mg/kg and 5/10 male rats receiving 500 mg/kg died before scheduled necropsy. After 13 weeks of treatment at 500 mg/kg, the final mean body weights relative to those of controls were depressed 16% in males and 8% in females. The liver was identified as the target organ with centrilobular congestion and necrosis noted in some animals given 1000 mg/kg but not at lower dose levels.

The fate in rats of a 4 mg/kg gavage dose of radiolabeled DCP, a dose much lower than that used for the more recent toxicity studies, has been reported by Hutson et al. (1971). Over 90% of the radioactivity of the 4 mg/kg dose was recovered within 24 hours in urine (50%), expired air (40%) and feces (4%). Overall recovery after 4 days was essentially 100%. Approximately 20% of the expired dose was carbon dioxide, the remainder was parent material and other related structures. Jones and Gibson (1980) reported that DCP was oxidized to the mercapturic acid N-acetyl-S- (2-hydroxypropyl) cysteine and excreted in the urine.

Our laboratory conducted acute studies on Fischer 344 rats employing evoked potential methodology to assess potential effects of DCP on selected electrophysiologic functions (Gorzinski, 1989). Parameters evaluated were the electroencephalogram (EEG), somatosensory (SEP) and cerebellar (CER) evoked potentials, and an assessment of the integrity of the visual pathways through the use of flash-evoked potentials (FEPs). Body temperature was recorded concurrently with all electrophysiologic tests.

Rats given single doses of 25, 50 or 100 mg DCP/kg bw had decreased body temperature of 1° to 1.5 ° C when measured approximately 1 hour post-gavage. SEPs were evaluated for approximately 90 minutes post-gavage, and the 50 and 100 mg/kg doses produced acute transient changes in the SEP that were slight to moderate in degree. Blinking, tearing and lethargy were also noted during this time. The FEP's could not be evaluated because the tears clouded the eyes and the animals often kept their eyes closed. Other rats were given DCP at 100 or 200 mg/kg/day for up to 7 days. The acute clinical manifestations were most apparent on the first day and persisted only a few hours post-gavage. Acute signs were less with each subsequent daily dose, and were no longer apparent after about 4 days of treatment. One male rat and two female rats given 200 mg/kg had EEG and SEP evaluated for 1 hr after dosing on the seventh day. No clinical signs were noted, and only a slight change in SEP occurred in one female rat which also had a body temperature decrease of 1.4° C. The remaining two rats appeared unaffected except for a body temperature decrease of approximately 0.3° C.

In summary, electrophysiologic results from acute or 7-day dosing at up to 200 mg/kg/day did not identify a parameter that was consistently affected at a dose level devoid of potential systemic toxicity. Selecting doses in the range of those reported in extant literature to cause system toxicity would only confound interpretation of an electrophysiologic effect. Therefore, the approach of using altered electrophysiologic functions to set dose levels as outlined in the protocol was abandoned. Dose levels of 300 and 500 mg/kg were subsequently selected based on the clinical effects noted in the acute study, and literature data.

This study was conducted to meet the requirements of Good Laboratory Practice Procedures for Non-Clinical Studies (FDA,1978), the Environmental Protection Agency (EPA): TSCA Good Laboratory Practice Procedures (EPA, 1983), the EPA: TSCA Test Guidelines (EPA,1985) and the Standard Operating Procedures of the Dow Chemical Company Mammalian and Environmental Toxicology Research Laboratory.

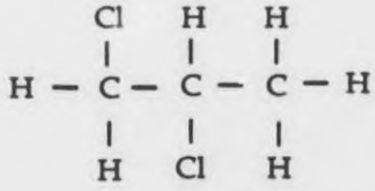
 Irrelevant, Filing Data

MATERIALS AND METHODS

General Study Design: Fischer 344 rats were randomly assigned to three groups of ten per sex and administered 0 (control, corn oil), 300 or 500 mg DCP/kg body weight/day via gavage for fourteen days. During the in-life portion of the study, data were obtained on clinical effects, body weights, functional observational battery, motor activity and body temperature. After 2 weeks, the rats were fasted overnight and submitted for necropsy. Serum was obtained and frozen for possible evaluation of clinical chemistries but this was never conducted. Blood was obtained for hematologic determinations, a gross examination conducted, and the liver, kidneys and spleen excised and the weights recorded. A complete set of tissues was saved for possible microscopic examination; however, histopathologic examination was performed only on sections of liver and kidney. Male and female rats were each dosed for 2 weeks, however, the female rats were started on test one day after the male rats to facilitate obtaining the data indicated.

Test Material and Dose Solutions: 1,2-Dichloropropane (CAS No. 78-87-5; DCP, lot No. 871112) was obtained from the Texas Division of The Dow Chemical Co., Freeport, TX. Analyses for purity indicated 99.9% 1,2-DCP with no impurities present at 0.05% or greater (Gerhart and Schlesinger (1988).

The structure and selected physical properties are listed below:



Appearance:	Colorless liquid
Molecular Weight:	112 Daltons
Vapor Pressure:	50 mm Hg @ 25°C
Boiling Point:	95-96°C
Flash Point:	40°C

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Concentrations of 5 and 500 mg DCP/ml of corn oil have been shown to be stable for at least 37 days (Krapscott, 1988). Dose solutions for the study were prepared fresh approximately every 2 to 3 days throughout the study. Solutions were submitted on three occasions and analyzed for concentration to confirm proper mixing. Male and female rats were dosed based on the weekly average group body weight. The doses were given to the rats via intubation needles (Popper & Sons, New Hyde Park, N.Y.) fitted to glass syringes.

Animals and Husbandry: Fischer 344 rats, six weeks of age, were purchased from the Charles River Breeding Laboratory, Kingston, New York. This strain of rat was chosen because of its general acceptance in neurotoxicity testing, availability of historical data and a reliable commercial supplier. Shortly after arrival at the laboratory[1] the animals were checked for health status by a veterinarian and acclimated to the laboratory environment according to Standard Operating Procedures. Rats were housed one per cage in suspended stainless steel cages which had wire-mesh floors. Catch pans under cages were lined with antibiotic impregnated absorbent deotized animal cageboard (Shepard Specialty Papers, Kalamazoo, MI) to minimize odor and maintain a clean environment. Animal cages were washed and cageboards changed regularly in accordance with good husbandry practices. All cages contained a food crock and a pressure-activated steel water nipple. The animal rooms of the testing facility were designed to maintain adequate environmental conditions concerning temperature, humidity, and photocycle, and were regulated for the species under test.

Purina Certified Rodent Chow (#5002) and municipal drinking water were available ad libitum throughout the study. Analysis of the Purina Certified Chow was performed by the Ralston Purina Company to confirm that the diet provided adequate nutrition, and to quantify the levels of selected contaminants. Analysis of the tap water was performed according to the

[1]Fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Standard Operating Procedures of the Mammalian and Environmental Toxicology Research Laboratory.

Study Conduct:

Clinical Observations: Cage-side observations for general health status were conducted twice daily in addition to examining the animals during the daily dosing procedure.

Body Weights: Body weights were recorded at least weekly and on the days that motor activity was evaluated. The body weight data were recorded using the laboratory computer system.

Functional Observational Battery--A detailed FOB (Table 1) was conducted preexposure and at 1hr, 6hr, and 24hr after the first dose. The FOB was also conducted prior to the daily dose on days 7 and 14. An assessment of grip strength, an adjunct evaluation typically included with the FOB, was not conducted during the 2-week study. The FOB consisted of a careful examination of all animals by the same technician. The handler presented the rats to the observer in a random order and in such a way that the observer did not know the identity of the rat nor the exposure level. The random order was provided by a computer-generated randomization scheme. Observations noted included: (a) any unusual responses with respect to body position, activity level, coordination of movement, and gait; (b) any unusual or bizarre behavior including but not limited to headflicking, head searching, compulsive biting or licking, self-mutilation, circling, and walking backwards; (c) the presence of convulsions, tremors, increased levels of lacrimation and/or red-colored tears, increased levels of salivation, piloerection, pupillary dilation or constriction, unusual respiration (shallow, labored, dyspneic, gasping, and retching) and/or mouth breathing, diarrhea, excessive or diminished urination, vocalization; (d) sensory function (audition, touch and pain perception).

Motor Activity: Motor activity was conducted approximately 30 minutes post-dosing on day 14 using a plexiglass circular alley (doughnut shaped) with

approximate dimensions: alley width = 8.3 cm, a radius to center of alley of 10.5 cm and 12 cm in height. An infrared photobeam bisected the doughnut so that the beam crossed the alley in two locations. The device is similar to that of Richelle et al. (1967). Animals were tested in a counter-balanced design for a total of 50 minutes consisting of five 10-minute epochs.

Body Temperature: Rectal temperature of the rats was obtained preexposure and approximately 1 hour after dosing on day 13 using a small animal thermistor (Model #409A, Yellow Springs Instrument Co., Yellow Springs, Ohio).

Pathology: Following the final dose on day 14 the rats were fasted overnight and presented for necropsy. Each animal was weighed, anesthetized with methoxyflurane, and a blood sample was collected from the orbital sinus for possible clinical chemistry and hematologic determinations. Serum for clinical chemistries was frozen but not analyzed. The following hematologic parameters were determined: hemoglobin concentration, hematocrit, and the counts of red blood cells, white blood cells and platelets. Stained blood smears were also prepared for all animals but no further evaluations were made. Male rats were allowed to recover from anesthesia after the blood sample was obtained. Shortly after the collection of the blood sample, male rats were again anesthetized, while the female rats did not have the hiatus and were maintained at an anesthetic level. While the rats were anesthetized, the trachea was exposed and clamped and then the rat was euthanatized. A complete gross pathologic examination was made by a veterinary pathologist. As part of the necropsy examination, the eyes were evaluated in situ utilizing a moistened glass slide. The liver, kidneys, and spleen of all rats were weighed. After examination, the lungs were distended to their approximately normal inspiratory volume with neutral, phosphate-buffered 10% formalin solution instilled via the trachea. The nasal cavities were flushed via the pharyngeal duct in a similar manner. A complete set of tissues (Table 2) was collected from each animal and preserved in formalin. Sections of the liver and kidneys were processed, embedded in paraffin, sectioned at ~6μ and

stained with hematoxylin and eosin. The sections were examined light microscopically by a veterinary pathologist.

Statistical Analyses: The body weights, hematologic determinations and organ weights were evaluated by Bartlett's test for equality of variances. Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or nonparametric analysis of variance (ANOVA), followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Statistical outliers were identified by a sequential test.

The nominal alpha levels used and test references were as follows:

Bartlett's test (Winer, 1971)	$\alpha = 0.01$
Parametric ANOVA (Steel and Torrie, 1960)	$\alpha = 0.10$
Nonparametric ANOVA (Hollander and Wolfe, 1973)	$\alpha = 0.10$
Dunnett's test (Winer, 1971)	$\alpha = 0.05$, two-sided
Wilcoxon Rank-Sum test (Hollander and Wolfe, 1973)	$\alpha = 0.05$, two-sided
Bonferroni correction (Miller, 1966)	
Outlier test (Grubbs, 1969)	$\alpha = 0.02$, two-sided

Body temperature and motor activity data were analyzed by a factorial analysis of variance (ANOVA), using the GLM procedure of SAS (SAS Institute Incorporated, Carey, North Carolina) with $\alpha = 0.05$. The factors were treatment and sex. Treatment, sex, and the sex by treatment interaction were assessed. If a meaningful sex by treatment interaction was identified, the sexes would have been analyzed separately and contrasts reported. No meaningful interaction patterns were found, and contrasts of each treatment level versus control (using the overall variance/covariance structure) were further examined. Each variable was tested for homogeneity of variance at $\alpha = 0.01$ by the F-max test (Bruning and Kintz, 1977). If heterogeneity of variance had occurred and was attributable to one or two outlying data points, then these data would have been removed from parametric analysis and the data from these animals would be discussed separately. If removing one or

two data points did not eliminate heterogeneity of variance, then the variable would have been removed from analysis of variance and discussed as a separate statistical finding.

This was an exploratory study in which numerous measurements were statistically compared in the same group of animals. For this reason, the overall false positive rate (Type I error) could be greater than the cited alpha would suggest and a firm statement of statistical probability could not be made. The final interpretation of the numerical data considered statistical analyses along with other factors such as dose-response relationships and whether the results were meaningful in light of other findings.

RESULTS AND DISCUSSION

Dose Solution Analyses: The results of the analyses of the dose solutions are presented in Table 3. All dosing solutions were at least 90% of the targeted concentration with a range of 91% to 95% and confirmed that the mixing procedure was adequate for the concentrations selected.

Clinical Observations: All rats survived the 2-week dosing period. On the first day of dosing, DCP produced blinking, tearing, salivation, and lethargy (Table 4). Females also had decreased respiration. Blinking was the first clinical indication of a treatment effect, followed by tearing. Tearing was often profuse and the rats tended to keep their eyes closed. Treated rats also had decreased spontaneous locomotion and tended to huddle in a back corner of the cage. They were not anesthetized and could be prodded to move at which time they appeared quite alert and coordinated, but then reverted to dormancy. The symptomatology existed for approximately 4 hours and thereafter the animals appeared alert and had normal spontaneous locomotion. The rats adapted rapidly to succeeding doses such that the control and treated rats appeared comparable after the fifth dose. Although DCP produced a marked decrease in body weight for male rats, they were not unkempt in appearance at any time throughout the study.

Body Weights: The body weights of male rats given DCP were significantly decreased (Table 5) on the second day and by the 4th day a dose-dependent effect was apparent. After two weeks, the body weights of the 300 mg/kg group were decreased 11% below control whereas a decrease of 18% occurred in the 500 mg/kg dose group. Female rats given DCP did not have body weights that deviated significantly from controls when recorded at two weeks (Table 6). Those given 500 mg/kg did, however, have significant decreases in body weight for the majority of the study prior to the weights recorded on day 14. Thus, DCP at 300 or 500 mg/kg/day had a pronounced effect on the body weight of male rats whereas a mild, but generally statistically identified, effect was noted in female rats at the high dose level.

Functional Observation Battery: One hour after the initial dose all male rats given 300 mg/kg and 9 of 10 given 500 mg/kg had increased lacrimation (tears) and blinking of the eyes (Table 7). Increased salivation and reduced locomotion was noted in 3 male rats at 300 mg/kg and 2 at 500 mg/kg. Treated female rats were less affected than male rats. Decreased respiration was noted in four female rats of each treatment group (Table 8) but was not identified for male rats. Increased lacrimation was the most consistent clinical observation in treated rats. Recovery from the clinical effects was evidenced by the lack of noticeable effects at 6 hours, and subsequent uneventful observations at 24 hours, 7 days and 14 days.

Motor Activity: Evaluation of motor activity was conducted approximately 30 minutes post-dosing on day 14 of the study in an attempt to maximize a potential response. The time of approximately 30 minutes was selected to correspond with the treatment response noted for the clinical observations following the first dose. No statistically significant differences between control and treated animals were noted for either male or female rats (Figure 1, males; Figure 2, females; Table 9). Female rats, however, exhibited a dose-related trend for reduced activity.

Body Temperature: Body temperature was taken approximately 1 hour post-gavage on day 13 of the study because of the decrease noted at dose levels of 25 to 100 mg/kg in the acute probe when electrophysiologic tests were conducted. Preexposure and 13-day body temperatures for male and female rats are presented in Table 10 and show decreased body temperature at 13 days for all groups of rats given DCP. The temperature decrease was approximately 0.5° C at 300 mg/kg and 0.3° C at 500 mg/kg for both male and female rats given DCP. These differences are less than the daily variation (circadian) in body temperature and do not follow a dose-response pattern, therefore these changes are of questionable toxicological significance.

Pathology: Two male rats each from the 300 or 500 mg DCP/kg/day groups died spontaneously from anesthetic overdose in the short interval between blood sampling and necropsy. This did not affect the hematologic parameters,

gross observations or histopathologic examinations of tissues from these animals. However, these four animals failed to exsanguinate completely and their organ weights were not recorded.

There were no effects on hematologic parameters considered to be of toxicologic significance (Tables 11 and 12). Platelet numbers were statistically identified as being decreased for male rats given 300 or 500 mg/kg/day. Female rats receiving 500 mg/kg/day were noted to have statistically identified increased total white blood cell counts. Both of these effects were of minor degree and were confined to only one sex. They are considered to be due to normal variability. Male rats receiving 300 mg/kg/day had a statistically identified mild increase in RBC number. This also is regarded as due to random variability as this does not follow a dose-response pattern.

There were no gross pathologic observations noted at necropsy that were suggestive of a specific target organ (Table 15). Only a very few observations were noted and, in all cases, the observations were made for only a single rat. The erosions of the glandular mucosa of the stomach noted for one male rat receiving 500 mg/kg/day are likely a secondary effect of stress.

Terminal body, organ and organ/body weight ratios are reported in Tables 13 and 14 for males and females, respectively. Rats of either sex receiving 500 mg/kg/day and males receiving 300 mg/kg/day had significantly decreased body weight. Males were more affected than females with terminal body weights decreased about 16% for males and 5.5% for females receiving 500 mg/kg/day. In spite of the markedly decreased body weight for males, the absolute weights of the liver and kidneys were similar to controls. Therefore, the relative weights of these organs were significantly increased. For females with the smaller decreases of body weight, the liver and kidney weights were statistically identified as increased on both an absolute and a relative basis for both the 300 and 500 mg/kg/day dose groups. The spleen of treated rats tended to weigh less than the controls and the absolute spleen weight was statistically identified as decreased for both sexes receiving 500 mg/kg/day and males receiving 300 mg/kg/day. The hemolytic anemia noted by Bruckner

et al. (1988) and MacKenzie et al. (1987) for Sprague-Dawley rats was accompanied by marked increases in the spleen weight at dose levels as low as 250 mg/kg/day. The increased spleen weight in their studies was secondary to the hemolytic anemia (due to red blood cell destruction and extramedullary hematopoiesis in the spleen). Thus, the absence of increased spleen weights in the present study is not surprising given the lack of effects on the red blood cells.

Histopathologic changes attributed to treatment were restricted to the liver and were noted for both males and females receiving either 300 or 500 mg/kg/day (Table 16). The changes were relatively mild and were characterized by prominent nucleoli of the hepatocytes in the centrilobular region of the hepatic lobule and degeneration and necrosis of individual hepatocytes accompanied by a few inflammatory cells in this region (Figure 2). The prominent nucleoli were noted for all rats receiving 500 mg/kg/day and for 8 of 10 rats of each sex receiving 300 mg/kg/day. The individual cell necrosis was noted for about one-half of the rats in each dose group. Similar effects were reported by MacKenzie et al. (1987) and Bruckner et al. (1988) They reported that rats may develop a resistance to hepatic effects with repeated dosing. They found hepatic effects at dose levels as low as 100 mg/kg/day after 10 days of dosing. However, after 90 days of dosing, similar effects were noted only at 500 mg/kg/day with no hepatic effects noted at 250 mg/kg/day.

In spite of the increase in kidney weights, there were no treatment-related histopathological effects noted in this organ. MacKenzie et al. (1987) and Bruckner et al. (1988) reported no primary effect of DCP upon the kidneys of Sprague-Dawley rats although they did note increased amounts of iron-containing pigment in the renal tubular cells secondary to the hemolytic anemia. The lack of any similar renal pigment in the Fischer 344 rat is consistent with the previously noted lack of effects upon the red blood cells.

CONCLUSIONS

Gavage administration of 300 or 500 mg/kg/day of DCP to groups of ten rats per sex for 2 weeks produced treatment effects on demeanor manifested primarily as tearing, blinking and lethargy. These were pronounced following dosing only for the first few days of the study and thereafter control and treated rats appeared comparable. Other than these transient clinical effects, other treatment-related effects were generally of greater degree in male rats. Body weights, both during the study and at termination, of both groups of treated male rats were significantly decreased whereas only the high dose female rats had slightly decreased body weight.

The body temperature of male and female rats given either 300 or 500 mg/kg DCP was decreased 0.3-0.5° C when recorded approximately 1 hour after dosing on day 13. No effect was seen on motor activity of either sex when evaluated approximately 0.5 hour after dosing on day 14. There were no effects on hematologic parameters considered related to treatment. Relative (g/100g) liver and kidney weights were increased in a general dose response manner for treated rats of either sex. Also, spleen weights were decreased in treated rats, particularly males. The decreased spleen weights were considered a nonspecific secondary effect of stress.

Histopathologic changes attributed to treatment were confined to the liver and noted for both males and females given either 300 or 500 mg DCP/kg/day. The changes were mild and were characterized by prominent nucleoli of the hepatocytes in the centrilobular region of the hepatic lobule, degeneration, and necrosis of individual hepatocytes accompanied by a few inflammatory cells. No microscopic effects were noted in the kidneys.

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J. E. Battjes	Clinical Chemistry
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D. J. Schuetz	Histology
A. J. Wall	Analytical Support
S. K. Weiss	Data Management

SIGNATURES

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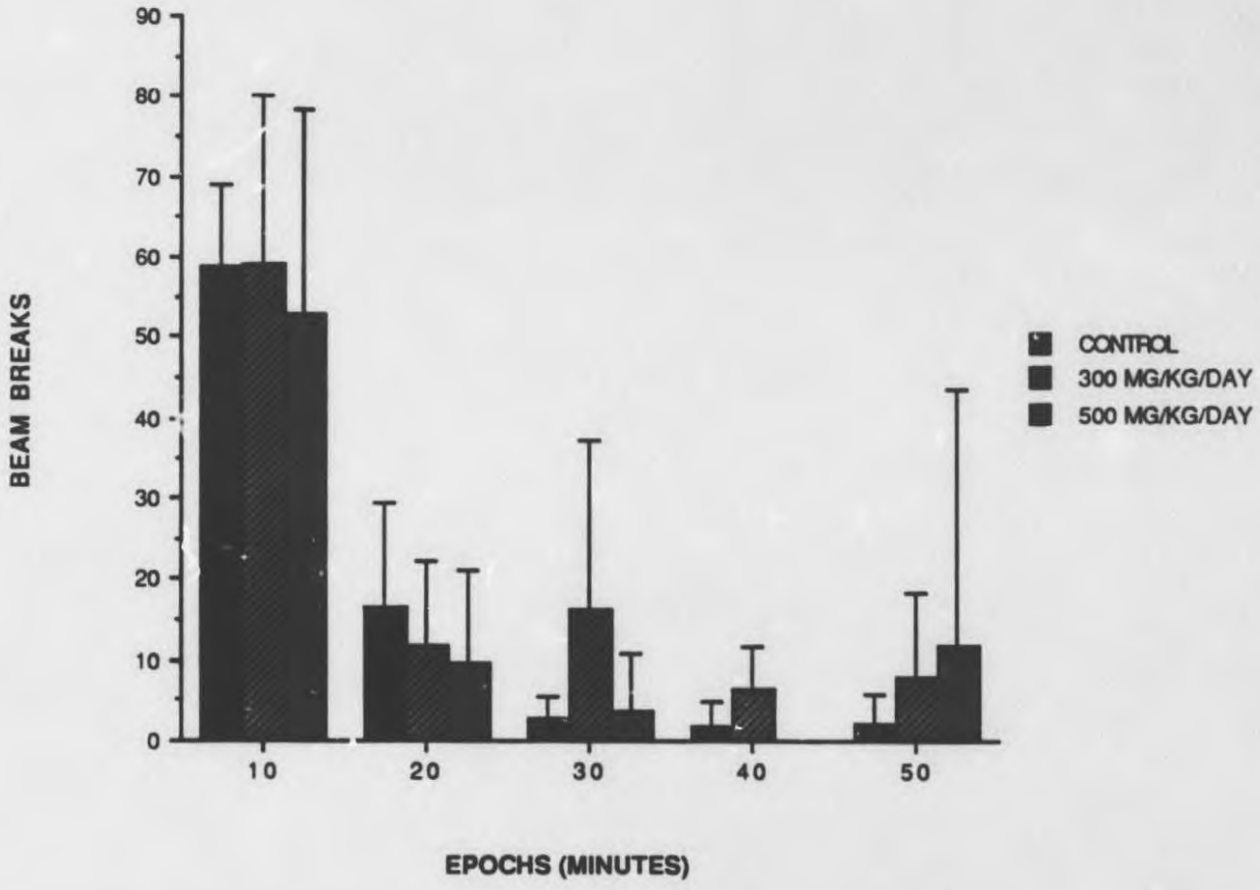
NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS

FIGURE 1

MALE MOTOR ACTIVITY - 14 DAY



NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS

FIGURE 2

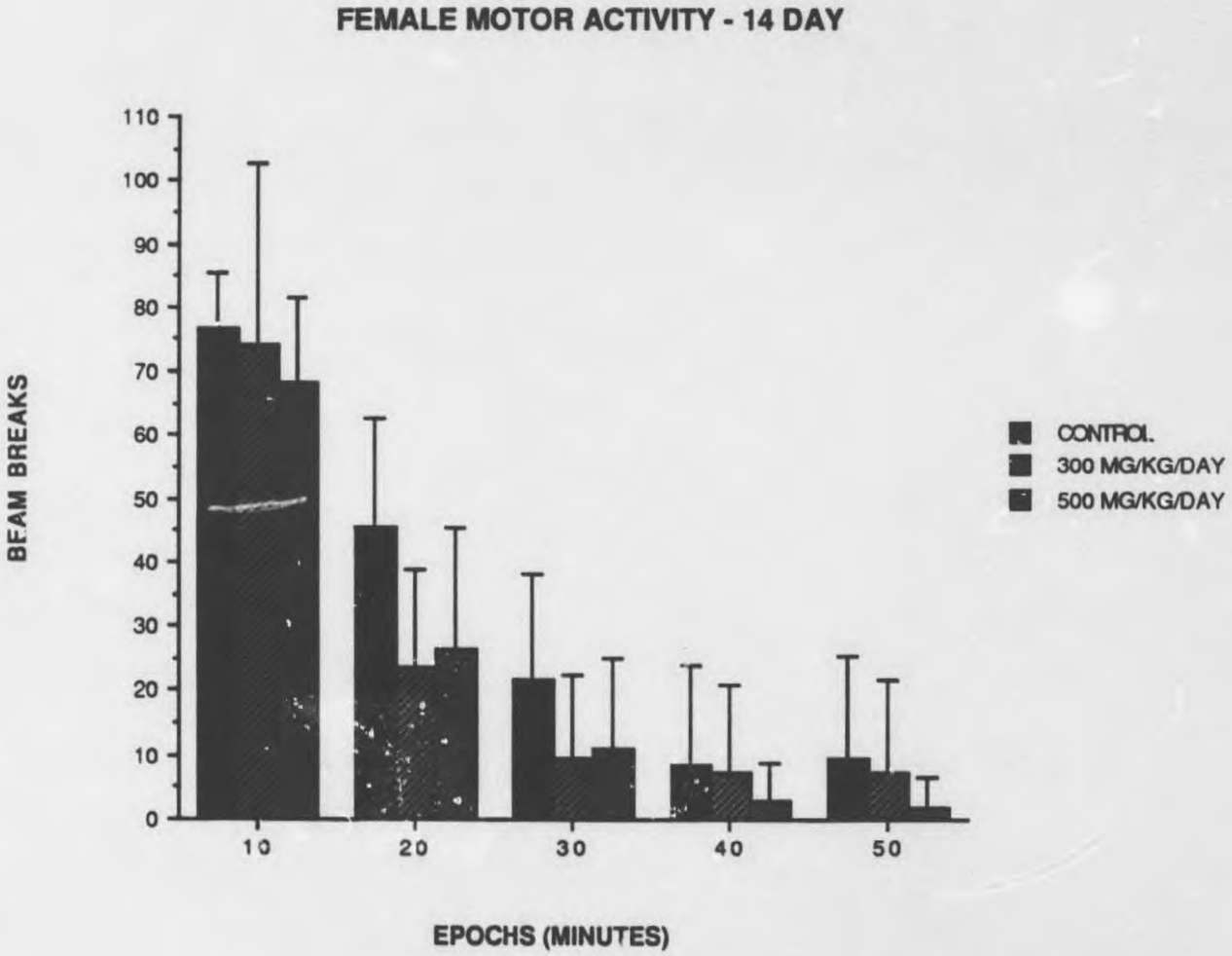
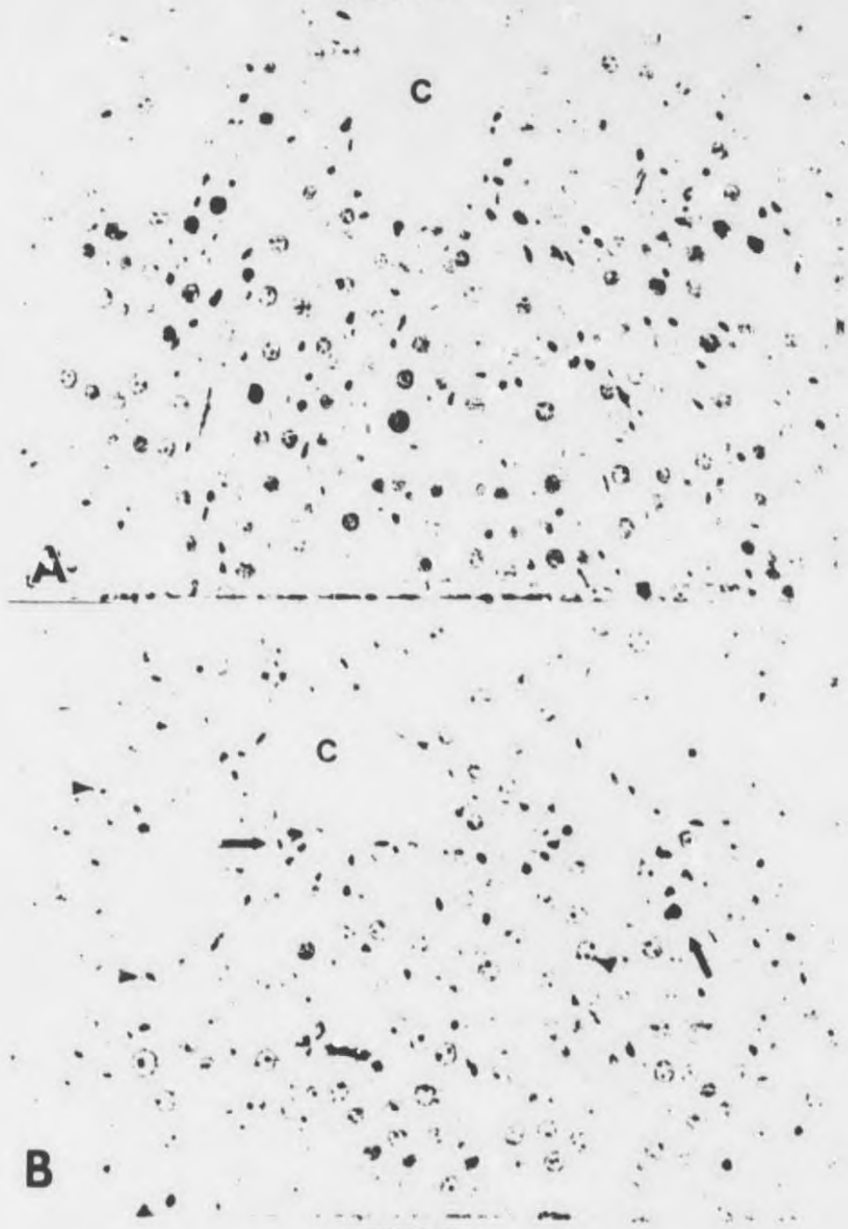


FIGURE 3



LEGEND

Figure 1. Photomicrographs of centrilobular region of the liver from a control animal (A) and a male rat receiving 500 mg/kg/day for 2 weeks (B). There is degeneration and necrosis of individual hepatocytes with localized inflammatory cell infiltrate (arrows). The nucleoli of the hepatocytes in this region are enlarged (arrowheads). Central vein (C). H and E. 300X.

TABLE 1

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

FUNCTIONAL OBSERVATIONAL BATTERY (FOB)

Observations In Hand:	Parameter Recorded As:
Pupil Size	N, I, or D
Respiration (increased, wheezing, etc.)	N or A (Describe)
Movement (bizare behavior, tremors,convulsions, etc.)	N or A (Describe)
Skin and Haircoat (poor grooming,piloerection, etc)	N or A (Describe)
Salivation	N or I
Lacrimation	N or I
Urine Staining	+ or -
Fecal Staining	+ or -
Observations in 50 cm x 50 cm Clear Plastic Box:	
Locomotor Behavior (gait, activity level, coordination, etc.)	N or A (Describe)
Responsiveness to Touch	N, I, or D
Responsiveness to Sharp Noise	N, I, or D
Responsiveness to Tail Pinch	N, I, or D

N = Normal; I = Increased; D = Decreased; Des = Describe; - = Absent
+ = Present.

TABLE 2

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

TISSUES COLLECTED AND PRESERVED AT NECROPSY

ADRENALS
AORTA
AUDITORY SEBACEOUS GLANDS
BONE
BONE MARROW
BRAIN (CEREBRUM, BRAINSTEM, CEREBELLUM)
CECUM
CERVIX
COAGULATING GLANDS
COLON
DUODENUM
EPIDIDYMIDES
ESOPHAGUS
EYES
GROSS LESIONS
HEART
ILEUM
JEJUNUM
KIDNEYS
LACRIMAL/HARDERIAN GLANDS
LARYNX
LIVER
LUNGS
MAMMARY GLAND
MEDIASTINAL LYMPH NODE
MEDIASTINAL TISSUES
MESENTERIC LYMPH NODE
MESENTERIC TISSUES
NASAL TISSUES
ORAL TISSUES
OVARIES
OVIDUCTS
PANCREAS
PARATHYROID GLANDS
PERIPHERAL NERVE
PITUITARY
PROSTATE
RECTUM
SALIVARY GLANDS
SEMINAL VESICLES
SKELETAL MUSCLE
SKIN
SPINAL CORD (CERVICAL, THORACIC, LUMBAR)
SPLEEN
STOMACH
TESTES
THYMUS
THYROID GLAND
TONGUE
TRACHEA
URINARY BLADDER
UTERUS
VAGINA

TABLE 3

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

RESULTS CF ANALYSES OF DOSE SOLUTIONS@

	TARGETED CONCENTRATION (MG DCP/ML)		
DATE	0	300	500
1-29-88	ND#	278 ± 2	475 ± 4
1-30-88	ND	275 ± 2	460 ± 24
2-1-88	ND	274 ± 2	471 ± 14

@Values are mean ± S.D. for 2 aliquots analyzed/sample.
ND = Not detected at a detection limit of 1.9 ug/ml.

TABLE 4

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

INCIDENCE OF CLINICAL EFFECTS FOLLOWING THE FIRST FIVE DAYS OF DOSING@

	DAY OF STUDY	DOSE MG/KG/DAY 0	300	500
MALES	1	0	10	10
	2	0	6	8
	3	0	5	6
	4	0	2	4
	5	0	0	0
FEMALES	1	0	8	9
	2	0	4	6
	3	0	2	4
	4	0	2	3
	5	0	0	0

@ Clinical effects following dosing were generally blinking, tearing, decreased respiration and reduced locomotion. Values shown are number of rats responding out of a group size of 10.

TABLE 5

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

BODY WEIGHTS (G) - MALES

DOSE MG/KG/DAY		DAYS ON TEST - 1	1	2	4	8	9	11	14
0	MEAN	126.9	132.8	134.8	144.8	166.7	170.5	178.6	187.9
	S.D.	3.7	4.1	4.6	4.6	5.6	5.7	6.1	5.9
	N=	10	10	10	10	10	10	10	10
300	MEAN	127.2	133.5	125.6*	133.3*	151.5*	156.0*	161.0*	167.7*
	S.D.	3.8	5.1	5.5	6.4	8.2	8.7	8.8	10.1
	N=	10	10	10	10	10	10	10	10
500	MEAN	127.1	131.5	124.7*	129.1*	146.2*	149.6*	152.5*	155.1*
	S.D.	3.7	5.1	5.6	7.6	8.7	9.0	11.2	11.2
	N=	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.

TABLE 6

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

BODY WEIGHTS (G) - FEMALES

DOSE MG/KG/DAY		DAYS ON TEST - 2	- 1	1	3	7	8	10	13	14
0	MEAN	95.8	99.9	102.3	104.4	114.1	116.2	119.6	122.0	124.0
	S.D.	2.8	3.1	3.5	4.3	3.5	3.5	3.8	4.5	4.3
	N=	10	10	10	10	10	10	10	10	10
300	MEAN	95.7	100.8	103.4	101.2	111.9	114.4	118.4	121.2	122.7
	S.D.	3.0	2.6	3.3	3.4	3.9	3.3	5.1	5.2	6.0
	N=	10	10	10	10	10	10	10	10	10
500	MEAN	96.0	100.1	103.0	98.4*	108.6*	110.9*	113.7*	117.9	119.0
	S.D.	3.0	3.3	3.2	4.4	4.5	4.3	5.4	5.2	5.6
	N=	10	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.

 Irrelevant, Filing Data

TABLE 7

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -PRE EXPOSURE- MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; - = Absent; + = Present.

TABLE 7 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -1 HOUR POST DOSING- MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	0,10@	1,9@
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	7,3	8,2
Lacrimation (N,I)	10,0	0,10	1,9
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	7,3Δ	8,2Δ
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	9,0,1

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.
@= Eye blinking.
Δ= Reduced and/or uncoordinated.

TABLE 7 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -6 HOUR POST DOSING - MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10 0	9,1	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 7 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -24 HOUR POST DOSING - MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 7 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -7 DAY - MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 7 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPO. 'D
TO 1,2-DICHLOROPRO?ANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -14 DAY - MALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Des .ibe; -= Absent; + = Present.

TABLE 8

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS - PRE EXPOSURE - FEMALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 8 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -1 HOUR POST DOSING - FEMALES

	DOSE MG/KG/DAY		
	— —	300	500
Pupil Size (N,I,D,	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	6,4	4,6Δ
Movement (N,A)	10,0	10,0	9,1@
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	7,3	7,3
Lacrimation (N,I)	10,0	4,6	3,7
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	8,2	9,1
Touch (N,I,D)	10,0,0	10,0,0	9,0,1
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.
@Eye blinking.
Δ=Decreased respiration.

TABLE 8 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -6 HOUR POST DOSING - FEMALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	9,1
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 8 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS - 24 HOUR POST DOSING - FEMALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 8 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -7 DAY - FEMALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 8 (CONTINUED)

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF FOB OBSERVATIONS -14 DAY - FEMALES

	DOSE MG/KG/DAY		
	0	300	500
Pupil Size (N,I,D)	10,0,0	10,0,0	10,0,0
Respiration (N,A)	10,0	10,0	10,0
Movement (N,A)	10,0	10,0	10,0
Skin and Coat (N,A)	10,0	10,0	10,0
Salivation (N,I)	10,0	10,0	10,0
Lacrimation (N,I)	10,0	10,0	10,0
Urine staining (-,+)	10,0	10,0	10,0
Fecal Staining (-,+)	10,0	10,0	10,0
Locomotor Behavior (N,A)	10,0	10,0	10,0
Touch (N,I,D)	10,0,0	10,0,0	10,0,0
Noise (N,I,D)	10,0,0	10,0,0	10,0,0
Pinch (N,I,D)	10,0,0	10,0,0	10,0,0

Data are the number of rats with the specified observation in the order listed in the parenthesis after the observation.
N=Normal; I=Increase; D=Decrease; A=Abnormal-Describe; -= Absent; + = Present.

TABLE 9

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

MOTOR ACTIVITY TOTAL COUNTS@

	DOSE MG/KG/DAY		
SEX	0	300	500
Males	82±22	101±47	78±35
Females	162±52	122±65	110±44

@ Values are means and S. D. for 10 rats/group.
Motor activity recorded on day 14 of the study.

STATISTICAL ANALYSES (ANOVA) FOR MOTOR ACTIVITY

LEVEL	p VALUE
Treatment	0.1654
Sex	0.0005
Sex x Treatment	0.1126
0 vs 300 mg/kg	0.4710
0 vs 500 mg/kg	0.0613

TABLE 10

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

SUMMARY OF RECTAL BODY TEMPERATURE@

		DOSE MG/KG/DAY		
		0	300	500
PRE EXPOSURE				
	Males	37.8±0.3	37.7±0.3	37.7±0.2
	Females	37.8±0.2	37.7±0.2	37.7±0.2
DAY 13				
	Males	37.6±0.1	37.1±0.1	37.3±0.3
	Females	37.9±0.3	37.4±0.6	37.5±0.7

@Values are mean and S.D. for 10 rats/group. Temperature on day 13 was recorded approximately 1 hour after dosing.

STATISTICAL ANALYSES FOR RECTAL TEMPERATURES

	p VALUE	
LEVEL	PREEXPOSURE	DAY 13
Treatment	0.6665	0.0008*
Sex	0.7107	0.0246*
Sex x Treatment	0.9237	0.8943
0 vs 300	0.4371	0.0003*
0 vs 500	0.4371	0.0048*

*Statistically significant at alpha = 0.05.

TABLE 11

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED
TO 1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

HEMATOLOGY - MALES - 2 WEEKS

DOSE MG/KG/DAY		RBC X10E6 /CU|MM	HGB G/DL	HCT %	PLAT X10E3 /CU|MM	WBC X10E3 /CU|MM
0	MEAN	7.62	17.1	45.6	1025	7.5
	S.D.	0.94	2.0	5.6	38	1.0
	N=	10	10	10	10	10
300	MEAN	8.17$	18.1	48.0	947*	8.2
	S.D.	0.22	0.6	1.2	44	1.0
	N=	10	10	10	10	10
500	MEAN	8.01	17.5	46.6	934*	8.5
	S.D.	0.41	1.2	2.5	72	1.6
	N=	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.
$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA = 0.05.

TABLE 12

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

HEMATOLOGY - FEMALES - 2 WEEKS

DOSE MG/KG/DAY		RBC X10E6 /CU|MM	HGB G/DL	HCT %	PLAT X10E3 /CU|MM	WBC X10E3 /CU|MM
0	MEAN	7.87	17.5	47.2	1005	7.7
	S.D.	0.34	0.8	2.1	79	1.4
	N=	10	10	10	10	10
300	MEAN	8.09	17.7	48.6	1045	9.1
	S.D.	0.30	0.7	1.5	48	1.6
	N=	10	10	10	10	10
500	MEAN	7.80	16.7	46.4	1032	9.4*
	S.D.	0.33	0.8	1.8	68	1.5
	N=	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.

TABLE 13

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

ORGAN AND ORGAN/BODY WEIGHTS - MALES - 2 WEEKS

DOSE MG/KG/DAY		FINAL BODY WT.(G)	KIDNEYS (G)	KIDNEYS (G/100)	LIVER (G)	LIVER (G/100)	SPLEEN (G)	SPLEEN (G/100)
0	MEAN	163.6	1.297	0.792	5.150	3.148	0.354	0.217
	S.D.	5.4	0.074	0.029	0.275	0.125	0.014	0.007
	N=	10	10	10	10	10	10	10
300	MEAN	147.0*	1.276	0.868*	4.964	3.378*	0.309*	0.210
	S.D.	7.5	0.087	0.046	0.325	0.150	0.022	0.007
	N=	9	8	8	8	8	8	8
500	MEAN	137.7*	1.255	0.914*	5.081	3.694*	0.281*	0.204*
	S.D.	9.9	0.072	0.060	0.308	0.157	0.012	0.014
	N=	8	8	8	8	8	8	8

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.

TABLE 14

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

ORGAN AND ORGAN/BODY WEIGHTS - FEMALES - 2 WEEKS

DOSE MG/KG/DAY		FINAL BODY WT. (G)	KIDNEYS (G)	KIDNEYS (G/100)	LIVER (G)	LIVER (G/100)	SPLEEN (G)	SPLEEN (G/100)
0	MEAN	110.0	0.924	0.841	3.484	3.168	0.295	0.268
	S.D.	4.6	0.035	0.041	0.213	0.166	0.019	0.010
	N=	10	10	10	10	10	10	10
300	MEAN	107.7	0.990*	0.920*	3.917*	3.640*	0.280	0.259
	S.D.	5.1	0.031	0.044	0.133	0.116	0.020	0.011
	N=	10	10	10	10	10	10	10
500	MEAN	104.0*	1.003*	0.966*	4.229*	4.068*	0.270*	0.260
	S.D.	4.1	0.040	0.038	0.223	0.143	0.015	0.010
	N=	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA = 0.05.

TABLE 15

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

GROSS PATHOLOGIC OBSERVATIONS@

SEX	MALES			FEMALES		
DOSE IN MG/KG/DAY	0	300	500	0	300	500
NUMBER OF RATS EXAMINED	10	10	10	10	10	10
LIVER						
WITHIN NORMAL LIMITS.	10	10	10	9	10	10
HERNIA, LEFT MIDDLE LOBE, CRANIAL:	0	0	0	1	0	0
OVARIES						
WITHIN NORMAL LIMITS.	-	-	-	10	9	10
DISTENDED, OVARIAN BURSA, UNILATERAL:	-	-	-	0	1	0
STOMACH						
WITHIN NORMAL LIMITS.	10	10	9	10	10	10
EROSION(S), GLANDULAR MUCOSA, MULTIFOCAL:	0	0	1	0	0	0
TESTES						
WITHIN NORMAL LIMITS.	10	10	9	-	-	-
DECREASED SIZE, UNILATERAL:	0	0	1	-	-	-
ALL OTHER TISSUES (COMPLETE NECROPSY PERFORMED)						
WITHIN NORMAL LIMITS.	10	10	10	10	10	10

@ DATA ARE THE NUMBER OF ANIMALS WITH THE SPECIFIED OBSERVATION.
- INDICATES NOT APPLICABLE.

TABLE 16

NEUROTOXICOLOGIC EXAMINATION OF FISCHER 344 RATS EXPOSED TO
1,2-DICHLOROPROPANE (DCP) VIA GAVAGE FOR 2 WEEKS
STUDY ID: K-002127-009B

HISTOPATHOLOGIC OBSERVATIONS@ -

SEX		MALES			FEMALES		
DOSE IN MG/KG/DAY		0	300	500	0	300	500
NUMBER OF RATS EXAMINED		10	10	10	10	10	10
KIDNEYS (NO. OF TISSUES EXAMINED)		10	10	10	10	10	10
WITHIN NORMAL LIMITS:		0	2	4	3	5	5
MINERALIZATION, TUBULE(S), MULTIFOCAL:	- VERY SLIGHT	8	8	6	6	3	5
THROMBUS - ACUTE OR RECENT, RENAL VEIN, FOCAL:		1	0	0	0	0	0
DEGENERATION/REGENERATION, TUBULE(S), FOCAL:	- VERY SLIGHT	2	0	1	2	1	0
DEGENERATION/REGENERATION, TUBULE(S), MULTIFOCAL:	- VERY SLIGHT	1	2	1	0	1	1
LIVER (NO. OF TISSUES EXAMINED)		10	10	10	10	10	10
WITHIN NORMAL LIMITS:		1	1	0	0	0	0
AGGREGATE(S) OF MONONUCLEAR (PREDOMINATELY LYMPHOID) CELLS, PERIPORTAL, FOCAL:	- VERY SLIGHT	2	2	0	0	0	0
AGGREGATE(S) OF MONONUCLEAR (PREDOMINATELY LYMPHOID) CELLS, PERIPORTAL, MULTIFOCAL:	- VERY SLIGHT	2	0	0	2	0	0
ARCHITECTURE ALTERED SECONDARY TO DIAPHRAGMATIC HERNIA, FOCAL:		0	0	0	1	0	0
FIBROSIS, SUBCAPSULAR, FOCAL:		1	0	0	0	0	0
NECROSIS - INDIVIDUAL CELL(S), CENTRILOBULAR:	- VERY SLIGHT	0	4	3	0	2	4
NECROSIS - INDIVIDUAL CELL(S), CENTRILOBULAR:	- SLIGHT	0	2	2	0	1	0
AGGREGATES OF RE CELLS FREQUENTLY ADJACENT TO DEGENERATIVE OR NECROTIC HEPATOCYTES, MULTIFOCAL:	- VERY SLIGHT	9	6	5	10	9	8
PROMINENT NUCLEOLI, CENTRILOBULAR:	- VERY SLIGHT	1	8	6	0	8	5
PROMINENT NUCLEOLI, CENTRILOBULAR:	- SLIGHT	0	0	4	0	0	5

@ DATA ARE THE NUMBER OF ANIMALS WITH THE SPECIFIED OBSERVATION.
- INDICATES NOT APPLICABLE.

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